

REMARKS

A check for the requisite fee for a three month extension of time accompanies this response. Any fee that may be due in connection with this application may be charged to Deposit Account No. Deposit Account No. 08-1641. If a Petition for extension of time is needed, this paper is to be considered such Petition. The fee for excess claims may be charged to Deposit Account No. 08-1641.

An unexecuted DECLARATION pursuant to 37 C.F.R. §1.132, with an attached exhibit (Little *et al.* (1997) "MALDI on a Chip: Analysis of Arrays of Low-Femtomole to Subfemtomole Quantities of Synthetic Oligonucleotides and DNA Diagnostic Products Dispensed by a Piezoelectric Pipet", Anal chem 69:4540-4546, which is of record in this application), is submitted herewith. The executed original will be submitted upon receipt.

Claims 1-6, 9-34, 40-51 and 54-101 are pending in this application. Claims 36-39, which are drawn to non-elected subject matter, are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional applications to the non-elected subject matter. Claims 8, 9, 35, 52 and 53 are also cancelled without prejudice or disclaimer. Claims 1, 3, 6, 11, 25, 27, 40, 70, 73, 76, 79 and 87 are amended herein. The amendments are designed to more particularly point out and distinctly claim the subject matter that applicant regards as the invention, and/or to correct apparent grammatical and typographic errors. The amended claims find basis in the specification and claims as originally filed. For example, claim 1 is amended by incorporation of the limitations of cancelled claims 7 and 8; and claim 25 is amended by incorporation of the limitations of cancelled claim 35; and claim 40 is amended by incorporation of the limitations of claims 52 and 53. Claims 91-96 are added and find basis in the specification as originally filed. Particular basis for claims 95-100 may be found, for example, at page 24, lines 24-26, which recites that "[t]he dispensed volume is controlled from 10^{-10} to 10^{-6} L by adjusting the

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

number of droplets dispensed." The dispensed volume produces spots that result from delivery of such volume. Therefore, no new matter has been added.

**THE REJECTION OF CLAIMS 25-30 and 73-79 UNDER 35 U.S.C. § 112,
SECOND PARAGRAPH**

Claims 25-30 and 73-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Various bases for this rejection are set forth and each is discussed in turn. Reconsideration of the grounds for rejection is respectfully requested in view of the amendments of the claims and the following remarks.

Relevant Law

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of prior art, and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Claims need only "reasonably apprise those skilled in the art" of their scope and be "as precise as the subject permits." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986), cert. den., 480 U.S. 947 (1987). The Court in Orthokinetics, Inc v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986) held that a claim limitation requiring that a paediatric wheelchair part be "so dimensioned as to be insertable through the space between the doorframe of an automobile and one of the seats" is definite. The Court stated:

The phrase 'so dimensioned' is as accurate as the subject matter permits, automobiles being of various sizes. As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, § 112, 2d ¶ requires nothing more. The patent law does not require that all possible lengths corresponding to the spaces in hundreds of different automobiles be listed in the patent, let alone that they be listed in the claims.

1 USPQ2d at 1088.

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

Analysis

The Examiner alleges that claim 25 is vague and indefinite for reciting "without contacting the surface with the vesicle" and lacks antecedent basis to what surface it refers.

First, the rejection for lack of antecedent basis is rendered moot by the amendment of claim 25, wherein the "surface" refers to the surface of the substrate.

Notwithstanding this, the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. "If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite." Ex parte Porter, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid").

Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface." M.P.E.P. § 2173.05(e).

Also, it is respectfully submitted that the meaning of "without contacting the surface with the vesicle" is taught in the present specification, and is clear and well known in the art. For example, in first paragraph of page 10, the present specification discloses that:

In the view shown by Fig. 1, it is also illustrated that the robotic assembly 16 can include a movable mount element 40 and a horizontal slide groove 42. The robotic arm 24 can optionally pivot about a pin 36 to increase the travel range of the arm 24 so that arm 24 can dispose the pin assembly 38 above source plate 20 (emphasis added).

Therefore, in view of Fig. 1 of the present specification, it is clear that the pin assembly, a type of vesicle, can be disposed without contacting the surface of the source plate, *i.e.*, the surface of the substrate. Further, the term is used in accord with the usual dictionary meaning. Thus, in accordance with the

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

amended claim 25, the vesicle is disposed without contacting, *i.e.*, touching, the surface of the substrate.

The Examiner states that "a" at line 3 (third occurrence) of claim 25 should be deleted. The rejection is obviated by the amendment of claim 25, by deleting "a".

The Examiner states that "the solvent" in claims 73, 76 and 79 lacks antecedent basis. The rejection is obviated by the amendment of claims 73, 76 and 79. The "solvent" is replaced with "fluid," which has antecedent basis in a base claim.

THE REJECTION OF CLAIMS 70, 71, 76, 79, 80 AND 84-86 UNDER 35 U.S.C. § 102(e)

Claims 70-71, 76, 79-80 and 84-86 are rejected under 35 U.S.C. § 102(e) as being anticipated by Ershow *et al.* U.S. Patent No. 5,756,050 because Ershow *et al.* discloses a method for dispensing nanoliter volumes of a material on the surface of a substrate by providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, each vesicle having a solid shaft of material having an end for retaining a nanoliter volume of fluid; loading a volume of fluid from a fluid source onto the end of the vesicles; disposing the pin assembly to align the vesicles at a first set of locations adjacent to the surface of the substrate; and contacting the loading fluid to the surface of the substrate aligned with the vesicles; whereby an array of material on the surface of the substrate is formed).

Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundsciber Corp. v.

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on Examiner to identify wherein each and every facet of the claimed subject matter is taught in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the claimed invention. An inherent property has to flow naturally from what is taught in a reference. In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The claims

Claim 70 is directed to a method for dispensing nanoliter volumes of a material as an array of spots of material on the surface of a substrate and analyzing the resulting material in the array by mass spectrometry. Claim 71 includes further steps of repeating certain steps specified in claim 70. Claims 76 and 79 further specify the nature of the fluid. Claim 80 includes a step for further analyzing the substrate array formed according to the method of claim 70. Claims 84-86 further specify the nature of the substrate.

Differences between the disclosure of Ershow *et al.* and claims 70-71, 76, 79-80 and 84-86

Each of claims 70-71, 76, 79-80 and 84-86 includes, as one element, analyzing the material in the resulting array by mass spectrometry. Ershow *et al.* does not disclose or suggest analysis of the array by mass spectrometry.

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

Since anticipation requires disclosure in a single reference of all elements as claimed, Ershow *et al.* does not anticipate any of the claims of 70-71, 76, 79-80 and 84-86 for failing to disclose the requisite step of analyzing the resulting array of material by mass spectrometry.

Furthermore, Ershow *et al.* does not teach or suggest the subject matter of these claims, because it does not teach or suggest the unexpected advantages for mass spectrometric analysis that result from the small size of the spots. These advantages, discussed in the specification, are also demonstrated in the attached DECLARATION, which is discussed below.

**THE REJECTION OF CLAIMS 1-35, 40-69, 72-75, 77, 78, 81-83 and 87-90
UNDER 35 U.S.C. § 103(a)**

Rejection over Tisone in view of Patterson

Claims 1-35, 40-69 and 87-90 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tisone, U.S. Patent No. 5,743,960 ("Tisone") in view of Patterson, U.S. Patent No. 5,869,240 ("Patterson") because Tisone is alleged to teach a method for dispensing a material on a substrate substantially similar to that as presently claimed. Tisone's method is alleged to comprise the steps of providing a vesicle having an interior chamber containing a fluid, disposing the vesicle adjacent to a first location on the surface of a substrate, controlling the vesicles to eject from the chamber a nanoliter volume of the fluid to dispense the fluid at the first location on the surface of the substrate, and moving the vesicle to a set of positions so that fluid is dispensed from the vesicle at each location of the set for forming an array of fluid material (figures 1, 6 and 7). Tisone is also alleged to teach that the method can be used to dispense sample fluids onto a diagnostic test strip for testing. It is acknowledged that Tisone does not teach or suggest the step of performing mass spectrometry analysis for the material. Nevertheless, it is alleged that such an analysis step is considered conventional in the art and is taught or suggested in Patterson. Patterson is alleged to teach a method for sequencing

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

polymers using a mass spectrometer in order to provide a rapid, automated and cost effective sequencing of polymers with a statistical certainty.

It is concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method and apparatus of Tisone with a spectrometer as taught in Patterson to provide a rapid, automated and cost effective sequencing of polymers with a statistical certainty.

The rejection is respectfully traversed insofar as it applies to any of claims 1-35, 40-69 and 87-90.

The Claims

Claims 1-24 and 87-90 are directed to methods for forming an array of a sample material on surface of a substrate. The methods include the steps of: providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material; disposing said vesicle adjacent to a first location of surface of a substrate without contacting the surface with the vesicle; providing mechanical pressure to the interior of the vesicle to eject from said chamber a nanoliter volume of the fluid to dispense said fluid at said first location of said surface of the substrate; moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a nanoliter volume of fluid is dispensed at each location of said set forming an array of sample material on the substrate; and performing mass spectrometric analysis of each sample.

Thus the method includes the step of providing mechanical pressure to the interior of the vesicle to eject from said chamber a nanoliter volume of the fluid to dispense said fluid at said first location of said surface of the substrate.

Dependent claims specify the material that is deposited, the types of vesicle and means for applying pressure, and additional method steps. For example, dependent claim 3 recites that the sample comprises a matrix material for mass spectrometry; claim 4 specifies that method further includes the step

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

permitting the sample with matrix material is dried onto the surface; claim 5 recites that the method of claim 4 further includes adding analyte to the dried matrix to form a crystalline structure on the substrate surface. Dependent claim 6 recites that the sample comprises a matrix material for mass spectrometry and analyte.

Claims 25-30 are directed to methods for analyzing a material by dispensing nanoliter volume fluid onto surface of a substrate using the steps of: providing a vesicle comprising a fluid containing the material in a solvent; disposing the vesicle adjacent to a first location of surface of a substrate without contacting the surface with the vesicle; delivering a defined and controlled nanoliter volume of the fluid at the first location of the surface of the substrate; moving the vesicle to a second position next to the first location on the surface of the substrate to dispense a defined and controlled volume of the material along an array of locations on the substrate surface to form an array of the material; and performing mass spectrometry analysis for the material at each location of the array.

Claims 31-34 are directed to the systems for forming an array of a sample material on surface of a substrate and for analyzing the array of sample material, which systems comprises: a vesicle having a distal end suitable for carrying a nanoliter of fluid; a movable arm having a distal portion mounted to move the vesicle; a controller for moving the arm to dispose the vesicle adjacent to a first location on the surface of the substrate and for controlling the vesicle to provide a nanoliter volume of the fluid at the first location of the surface of the substrate; and a mass spectrometer for analyzing the material deposited on the surface of the substrate by generating a composition signal representative of the chemical composition of the material.

Claims 40-69 are directed to methods for dispensing nanoliter volumes of a material as an array onto the surface of a substrate, comprising the steps of: (a) providing an assembly having a plurality of vesicles arranged in the form of array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material; (b) aligning the vesicles at a first set of locations adjacent to surface of a substrate without contacting the surface with the vesicle; (c) using mechanical pressure, controlling each of the chambers to eject a nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles; and (d) providing the resulting substrate with the array of material deposited thereon to mass spectrometer for determining information representative of the composition of the deposited material.

As with the other independent claims dependent claims specify the composition of the material that is deposited, the types of vesicle and means for applying pressure, and additional method steps.

Added claims 91-94, specify that the mass spectrometry format is MALDI; added claims 95-99 specify that the spots are of a size that results from dispensing a volume of 10^{-6} to 10^{-10} ; and claims 100 and 101 are directed to arrays produced by the methods.

The teachings of the cited references and differences from the claimed subject matter

Tisone

Tisone teaches a reagent dispensing apparatus including a positive displacement syringe pump in series with a solenoid valve dispenser. The pump is controlled by a stepper motor to provide an incremental quantity or continuous flow of reagent to the solenoid valve dispenser. The solenoid valve is opened and closed at a predetermined frequency and duty cycle to dispense droplets of reagent onto a target substrate at the metered flow rate.

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

Tisone also teaches that its apparatus can be used for aspirating ("sucking") precise quantities of reagent or other liquids from a sample or reservoir. At column 11, lines 17-21, Tisone states:

This mode may be used, for example, in a "suck and spit" operation whereby a precise quantity of fluid is aspirated from one vial containing a sample fluid and then dispensed into another vial or onto a diagnostic test strip for testing or further processing.

Tisone does not teach or even suggest, of all possible available technologies, which type of analytical technology can be used to analyze the sample transferred by the aspirating operation. Tisone certainly does not teach or even suggest that such sample can be analyzed by mass spectrometry, nor that improved performance can be achieved use of arrays produced by dispensing nanoliter volumes. }

Patterson

Patterson teaches integrated methods and apparatus for sequencing or identifying polymers by mass spectrometry with a statistical certainty. The methods involve integrating data obtained by mass spectrometry analysis of a series of polymer fragments and statistically comparing the data with hypothetical data corresponding to known sequences or identities. The statistical certainty does not derive from the format subjected to mass spectrometry, but from the algorithms and methodology used to analyze the data.

Patterson does not teach or suggest combining mass spectrometry analysis with arrays of samples produced by dispensing nanovolumes. Patterson does not teach or suggest that it is advantageous to perform mass spectrometry on an array of samples of a size that results from dispensing nanoliter volumes of material on a substrate. }

U.S.S.N. 08/786,988
LITTLE, et al.
AMENDMENT

The Office Action fails to set forth a case of *prima facie* obviousness

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The relevant standards and inquiries under 35 U.S.C. §103 were articulated by the U.S. Supreme Court in Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966):

[T]he scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the art resolved. Against this background, the obviousness of the subject matter is determined. Such secondary considerations as commercial

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Following Graham, the Court of Customs and Patent Appeals and its present successor the Court of Appeals of the Federal Circuit have held that the following considerations constitute objective evidence of non-obviousness which must be considered: long felt need, commercial success, failure of others, copying and unexpected results. *See, e.g., In re Sernaker*, 217 U.S.P.Q. 1 (Fed. Cir. 1983); *In re Imperato*, 179 U.S.P.Q. 730 (C.C.P.A. 1973). These courts have squarely held that if an applicant presents evidence relating to such objective indicia of non-obviousness, the Examiner or the Board must consider and cannot ignore such evidence, *In re Piasecki*, 233 U.S.P.Q. 785, 789 (Fed. Cir. 1984); *In re Sernaker*, 217 U.S.P.Q. at 7.

Evidence and arguments for overcoming rejections under 35 U.S.C. §103 need not be in specification. *In re Chu*, 36 U.S.P.Q.2d, 1089 (Fed. Cir. 1995) (held that "We have found no cases supporting the position that a patent applicant's evidence and/or arguments traversing a § 103 rejection must be contained within the specification. There is no logical support for such proposition as well, given that obviousness is determined by the totality of the record including, in some instances most significantly, the evidence and arguments proffered during the give-and-take of ex parte patent prosecution.").

It is respectfully submitted that Tisone and Patterson, whether alone or in combination, do not render the claimed subject matter prima facie obvious for the reasons set forth below.

(1) There would have been no motivation to have modified the teachings of Tisone with those of Patterson

The method claims set forth within the purview of this rejection include the element of analyzing the nanoliter volume samples dispensed on surface of

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT.

the substrate by mass spectrometry, and the system claims include a mass spectrometer as a necessary component. As discussed above, neither Tisone nor Patterson teaches or even suggests that such nanoliter volume samples can be analyzed by mass spectrometry. In one embodiment, Tisone teaches that its apparatus can be used for aspirating precise quantities of reagent or other liquids from a sample or reservoir and then dispensed into another vial or onto a diagnostic test strip for testing or further processing.

Tisone, whether alone or in combination, does not teach or even suggest, of all possible available technologies, which type of analytical technology, let alone mass spectrometry specifically, can be used to analyze the sample transferred by the aspirating operation.

(2) The combination of teachings of the cited references does not result in the instantly claims methods, substrates or systems

In addition, the combination of teachings of Tisone with those of Patterson does not result in the instantly claimed methods or systems. Furthermore, the combination of references does not teach or suggest the unexpected results that derive from using arrays produced by dispensing nanoliter volumes of sample for mass spectrometric analyses. The attached DECLARATION shows that when small volumes as described in the instant application are dispensed in arrays, the resulting spots are about the size of a focussed laser spot. The resulting mass spectra (see, *e.g.*, Figure 2 of the attached Exhibit, Little *et al.*) are uniform. They are far more uniform than spectra produced using arrays with larger spots.

As shown in the DECLARATION and attached paper and in the application, when larger conventional sample sizes (*e.g.*, 300 nL) are used, there is dramatic variability of analyte incorporation and ion yield. This results in the necessity to manually search within the resulting 1 to 2 mm diameter spots for regions from which intense signals can be obtained. This renders such arrays unamenable to automation, and also results in non-uniform spectra. The

variability in resulting spectra is too great for such arrays to be used in high throughput applications, such as DNA diagnostics that require automated handling and high reproducibility.

With the smaller spots, searching is unnecessary, since the laser spot covers the whole spot, permitting more rapid spectrum acquisition and more quantitative and uniform results. The arrays produced by dispensing nanoliter volumes result in uniform spectra, and, hence are suitable for use in applications requiring high reproducibility.

Unexpected properties

It is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole.

The presently claimed methods and systems possess unexpected properties not taught or suggested by the cited references

The presently claimed methods and systems possess unexpected, properties not taught by the cited references. For example, at page 23, first full paragraph, the present specification discloses:

[A] 'piezoelectric pipette' (70 μm id capillary) dispenses single or multiple -0.2 nL droplets of matrix, and then analyte onto the chip; spectra from as low as 0.2 fmol of a 36-mer DNA have been acquired using this procedure. Despite the fast (<5 sec.) evaporation, micro-crystals of 3-hydroxypicolinic acid matrix containing the analyte are routinely produced resulting in higher reproducibility than routinely obtained with larger volume preparation; all of 100 five fmol spots of 23-mer in 800 μm wells yielded easily interpreted mass spectra, with 99/100 parent ion signals having signal to noise ratio of >5 (emphasis added).

THE DECLARATION OF KÖSTER

The unexpected properties of the presently claimed methods and systems are further illustrated in the DECLARATION of Köster pursuant to 37 C.F.R. §1.132. Dr. Köster and his colleagues conducted the experiments presented in

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

the DECLARATION and in the paper Little *et al.*, which is attached to and part of the DECLARATION, as well as the above-described example in the application.

The results show that the sample array formed by the nanoliter dispensing methods has properties that are not taught or suggested by the cited references. The DECLARATION shows that spot-to-spot reproducibility from microdispensed samples is superior to that achieved using samples prepared by conventional pipetting. The DECLARATION demonstrates that the sample array formed by nanoliter volume dispensing methods having the above-described properties contributes to the shortened spectrum acquisition time (Declaration, paragraph 9), increased detection sensitivity (Declaration, paragraph 10) and makes sample handling far more routine and amenable to automation (Declaration, paragraph 11). When the miniaturized sample dispensing methods were used in dispensing biological samples, *e.g.*, dispensing samples generated in a temperature-cycled PROBE reaction (Little's Declaration, paragraphs 12-13), highly sensitive and accurate analysis could be achieved.

As a result the preparation of arrays of samples for mass spectrometric analysis, as taught in the present specification, permits highly accurate and reproducible mass spectrometric analyses to be performed. By virtue of the small spot size, there is a resulting high sample-to-sample uniformity of the sample spots, which can be entirely covered by the laser irradiation profile. This eliminates difficulties associated with nonuniform analyte incorporation and translates to a high spectrum acquisition spectrum reproducibility and high speed spectrum acquisition.

None of the cited reference singly or in combination teaches or suggests that small spot size is desirable for mass spectrometric analyses, nor that the result of such spot size leads to increased reproducibility in the results such that arrays of such spots can be used for analyses. Absent such reproducibility, arrays of samples would not be a suitable for mass spectrometric analyses, such as high throughput DNA diagnostics and sequencing.

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

Therefore, the presently claimed methods and systems achieve results *i.e.*, the shortened spectrum acquisition time, increased detection sensitivity, greater reproducibility, routine sample handling and amenability to automation that are not taught or suggested by the cited references.

Rejection over Ershow *et al.* in view of Patterson

Claims 72-75, 77-78 and 81-83 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ershow *et al.*, which teaches a tool for dispensing small volumes, in view of Patterson, which teaches method for sequencing using a mass spectrometer. The Examiner urges that use of a mass spectrometer to analyze an array of drops, presumably prepared using the dispensing tool of Ershow *et al.* would have been conventional in the art, and hence obvious.

This rejection is respectfully traversed.

Claims

Claims 72-75, 77-78 and 81-83 are directed to methods for dispensing nanoliter volumes of a material as an array on the surface of a substrate, comprising the steps of: (a) providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoliter volume of fluid; (b) loading a nanoliter volume of fluid comprising a liquid material from a fluid source onto the end of the vesicles of the pin assembly; (c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to surface of a substrate without contacting the surface with the vesicle; (d) dispensing the nanoliter volume of fluid without contacting the loaded fluid to the surface of the substrate aligned with the vesicles, whereby an array of material on the surface of the substrate is formed; and (e) analyzing the resulting arrays by mass spectrometry.

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

It is acknowledged that Ershow *et al.* does not teach or suggest the step of performing mass spectrometry analysis for the material. Nevertheless, it is alleged that such an analysis step is considered conventional in the art and taught in Patterson. Based on the above teachings, it is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method of Ershow *et al.* with a mass spectrometer as taught by Patterson to provide a rapid, automated and cost effective sequencing of polymers with a statistical certainty.

The rejection is respectfully traversed insofar as it applies to any of claims 72-75, 77-78 and 81-83.

Teachings of the cited references

The teachings of Ershow *et al.* and Patterson are discussed as above. As noted above, the statistical certainty alleged to be achieved by Patterson does not derive from the format subjected to mass spectrometry, but from the algorithms and methodology used to analyze the data.

Analysis

It is respectfully submitted that Ershow *et al.* and Patterson, whether alone or in combination, do not render the claimed subject matter prima facie obvious. Neither reference singly or in combination teaches the unexpected results achieved when arrays produced by dispensing nanoliter volumes are used in mass spectrometric analysis.

As discussed above and shown in the application, and the attached DECLARATION, the use of such arrays in mass spectrometric analyses results in decreased spectrum acquisition times, permits automation of the processes, and results in highly uniform and reproducible spectra. Such results are not taught or suggested in the cited references. The high reproducibility achieved using the instantly claimed methods does not derive from the paradigm used to analyze the data as in Patterson, but from the format in which the mass spectrometry

U.S.S.N. 08/786,988
LITTLE, *et al.*
AMENDMENT

analyses are performed. Therefore, the claimed subject matter is not prima facie obvious over Ershow *et al.* and Patterson, singly or in any combination thereof.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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